fragment does not cross react with 50μM of digoxin (*e.g.*, 5A12, A.T.C.C. Accession Number PTA-812), have been added. Support for new Claims 40-44 can be found, for example, in original Claims 1, 2, 5, 6, 38 and Figure 3 of the specification.

New Claims 45-55, which are directed to the specific monoclonal antibodies and hybridoma cell lines described in the subject specification. Support for new Claims 45-55 can be found, for example, in original Claims 1-6, 38 and 39 of the specification.

Rejection of Claims 2, 5 and 6 under 35 U.S.C. §101

Claims 2, 5 and 6are rejected under 35 U.S.C. §101 "because the disclosed invention is inoperative and therefore lacks utility" (Office Action, page 2). The Examiner states that the "specification teaches that antibody 5A12 cross reacts with digoxin" and that "although the specification teaches that antibody 1-10 and 8E4 do not cross react with digoxin, a review of Figure 6 reveals that at 70 μM concentration of digoxin, both the binding of antibody 1-10 and antibody 8E4 to Oua-BGG are inhibited by digoxin and therefore each antibody is cross reacting with digoxin" (Office Action, page 3). In addition, the Examiner states that "although the specification states that there is no cross reactivity of antibody [7-1] with digoxin at 100 μM concentration (see Table I), the specification states that the activity of antibody 7-1 and 1-10 are essentially identical and given the cross reactivity found at 70 μM for monoclonal antibody 1-10, it is expected that monoclonal antibody 7-1 also cross reacts with digoxin at that concentration" (Office Action, page 2-3).

As amended, Claims 1, 5 and 6 are directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin.

In response to the Examiner's comments regarding Figure 6, Applicants are filing herewith a Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132 (the Declaration). As Dr. Garner explains in the Declaration, a statistical analysis ("two-tailed T test") was applied to the raw data used to generate the graph of Figure 6. The statistical analysis showed that the "digoxin values clustered at the highest point in Figure 6 are in fact not different from zero inhibition" (the Declaration, page 3). Therefore, Figure 6 reveals that at 70 μM concentration of

digoxin, both the binding of antibody 1-10 and antibody 8E4 to Oua-BGG are not inhibited by digoxin, and thus, each antibody does not cross react with digoxin.

New Claims 40-43 are directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 50μM of digoxin, such as 5A12 (A.T.C.C. Accession Number PTA-812) or an antigen binding fragment thereof; a monoclonal antibody having the same binding specificity as 5A12; a hybridoma cell line which produces the 5A12 monoclonal antibody or a monoclonal antibody having the same binding specificity as 5A12; and a pharmaceutical composition thereof. Support for the new Claims 40-43 can be found, for example, in Figure 3. As shown on the x-axis of Figure 3, monoclonal antibody 5A12 has binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by about 50μM of digoxin.

As amended, Applicants' claimed invention is operative and, thus, possesses utility.

Rejection of Claims 2, 5 and 6 under 35 U.S.C. §112, first paragraph

Claims 2, 5 and 6 are rejected under 35 U.S.C. §112, first paragraph as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention" (Office Action, page 3). The Examiner states that, as set forth above, the claimed "embodiments are inoperative," and therefore, "one of skill in the art would not know how to use the claimed invention with a reasonable expectation of success" (Office Action, page 3).

Applicants respectfully disagree. As pointed out above, as amended, Claims 1, 5 and 6 are directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin.

Applicants direct that Examiner's attention to the Declaration wherein Dr. Garner explains that a statistical analysis ("two-tailed T test") of Figure 6 showed that the "digoxin values clustered at the highest point in Figure 6 are in fact not different from zero inhibition" (the Declaration, page 3). Therefore, Figure 6 reveals that at 70 μM concentration of digoxin, both

the binding of antibody 1-10 and antibody 8E4 to Oua-BGG are not inhibited by digoxin, and thus, each antibody does not cross react with digoxin.

New Claims 40-43 are directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 50μM of digoxin, such as 5A12 (A.T.C.C. Accession Number PTA-812) or an antigen binding fragment thereof; a monoclonal antibody having the same binding specificity as 5A12; a hybridoma cell line which produces the 5A12 monoclonal antibody or a monoclonal antibody having the same binding specificity as 5A12; and a pharmaceutical composition thereof. Support for the new Claims 40-43 can be found, for example, in Figure 3. As shown on the x-axis of Figure 3, monoclonal antibody 5A12 has binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by about 50μM of digoxin.

Applicants have provided an enabling disclosure for the full scope of Claims 2, 5 and 6, particularly as amended, and new Claims 40-43.

Rejection of Claims 2, 5 and 6 Under 35 U.S.C. §112, first paragraph

Claims 2, 5 and 6 are rejected under 35 U.S.C. §112, first paragraph "as failing to provide an adequate description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g., sequenced); or (3) deposited" (Office Action, page 3-4). The Examiner states that "[i]t is unclear if a cell line which produces an antibody having the exact structural and chemical identity of 1-10, 5A12, 7-1, 8E4 and antigen binding fragments thereof is known and publically available, or can be reproducibly isolated without undue experimentation" (Office Action, page 4). The Examiner further states that "Applicant's referral to a deposit of the cell lines wherein no deposit numbers are included on page 8 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01(p)(c) met" (Office Action, page 4). The Examiner requires compliance with deposit practice.

The A/J mouse spleen B cell hybridoma cell lines 1-10, 8E4, 5A12 and 7-1 have been deposited under the provisions of the Budapest Treaty with the ATCC accession numbers PTA-

814, PTA-815, PTA-816 and PTA-817, respectively, and the specification has been amended as required by 37 C.F.R. 1.809(d). Statements under 37 C.F.R. 1.806 and 1.808 are being filed concurrently, thereby completing the formal requirements for biological deposit. In addition, a copy of the A.T.C.C. receipt of the original deposits and viability statement are being filed concurrently.

Thus, the rejection under 35 U.S.C. §112, first paragraph is obviated.

Rejection of Claims 1, 3, 4, 38 and 39 Under 35 U.S.C. §112, first paragraph

Claims 1, 3, 4, 38 and 39 are rejected under 35 U.S.C. §112, first paragraph, as "containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 6-7). The Examiner states that "the data presented in the specification clearly shows that the antibodies exemplified do minimally cross react with digoxin" (Office Action, page 7). The Examiner states that the instant disclosure "does not adequately describe the scope of the claimed genus, which encompasses all antibodies that do not cross react with digoxin" (Office Action, page 7).

Applicants respectfully disagree. As pointed out above, as amended, Claims 1, 5 and 6 are directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin. Claims 5 and 6 have also been amended to indicate that the antibody binds ouabain and binding of the antibody to ouabain is not inhibited by about 50μM digoxin

Applicants direct that Examiner's attention to the Declaration wherein Dr. Garner explains that a statistical analysis ("two-tailed T test") of Figure 6 showed that the "digoxin values clustered at the highest point in Figure 6 are in fact not different from zero inhibition" (the Declaration, page 3). Therefore, Figure 6 reveals that at 70 μM concentration of digoxin, both the binding of antibody 1-10 and antibody 8E4 to Oua-BGG are not inhibited by digoxin, and thus, each antibody does not cross react with digoxin.

New Claims 40-43 are directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen

binding fragment to ouabain is not inhibited by about 50μM of digoxin, such as 5A12 (A.T.C.C. Accession Number PTA-812) or an antigen binding fragment thereof; a monoclonal antibody having the same binding specificity as 5A12; a hybridoma cell line which produces the 5A12 monoclonal antibody or a monoclonal antibody having the same binding specificity as 5A12; and a pharmaceutical composition thereof. Support for the new Claims 40-43 can be found, for example, in Figure 3. As shown on the x-axis of Figure 3, monoclonal antibody 5A12 has binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by about 50μM of digoxin.

At the time the application was filed, Applicants clearly had possession of a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin (*e.g.*, 1-10, 7-1 and 8E4) and a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 50μM of digoxin (*e.g.*, 5A12).

Rejection of Claims 2, 5 and 6 Under 35 U.S.C. §112, second paragraph

Claims 2, 5 and 6 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention" (Office Action, page 8). The Examiner states that the claims are "indefinite in the recitation of antibodies 1-10, 5A12, 7-1 and 8E4 as the sole means of identifying the claimed antibody" (Office Action, page 8). The Examiner further states that the use of laboratory designations to identify a cell line "renders the claims indefinite because different laboratories may use the same laboratory designations to define completely different hybridomas and antibodies" (Office Action, page 8). The Examiner then states that "Amendment of the claims to include depository accession number of the mAb or hybridoma is required, because accession numbers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody" (Office Action, page 8).

Applicants respectfully disagree. The meaning of a claim is not analyzed in a vacuum, but in light of the teachings in the specification (*In re Moore and Janoski*, 169 U.S.P.Q. 236, 238

(CCPA 1971). There is no requirement that the accession number be recited in the claims. 37 C.F.R. 1.809(d) states:

> For each deposit made pursuant to these regulations, the *specification* shall contain:
> 1. The accession number for the deposit;
> 2. The date of the deposit;
> 3. A description of the deposited biological material sufficient to specifically identify it and to permit examination; and
> 4. The name and address of the depository (Emphasis added).

Nevertheless, in order to expedite prosecution, Claims 2, 5 and 6 have been amended to recite the A.T.T.C. Accession Numbers for antibodies 1-10, 5A12, 7-1 and 8E4.

Rejection of Claims 1, 3, 4 and 39 under 35 U.S.C. §102(b)

Claims 1, 3, 4 and 39 are rejected under 35 U.S.C. §102(b) as being anticipated by Lin *et al.* (PNAS, 22:129-134 (1998)). The Examiner states that "Lin *et al.* teach a monoclonal antibody with binding affinity for ouabain wherein the antibody specifically and selectively binds ouabain...in human serum sample, wherein the presence of ouabain in human serum is demonstrated" (Office Action, page 9). The Examiner further sates that "Lin *et al* make clear the separability of ouabain and digoxin assays wherein they teach an antibody and immunoassay to digoxin in human serum, wherein it is demonstrated that human serum contains endogenous digoxin" (Office Action, page 9). The Examiner then states that "Although the [Lin] reference does not specifically teach that the ouabain monoclonal antibodies do not cross react with digoxin and that they have the binding affinities as claimed, the claimed antibodies appear to be the same as the prior art antibodies, absent a showing of obvious differences" (Office Action, page 9). Finally, the Examiner states that the "office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structure and functional characteristics of the claimed product" (Office Action, page 9).

Applicant's respectfully disagree. Lin *et al.* do ***not*** demonstrate specificity for ouabain and it is likely that the monoclonal antibody (mAb) of Lin *et al.* recognizes BSA. Furthermore, the factual evidence of record establishes that the Lin *et al.* monoclonal antibody does not possess the same material, structure and functional characteristics of Applicants' claimed

monoclonal antibody based on the different methods Lin *et al.* and Applicants employed to obtain the antibody.

Lin *et al.* injected Balb/C mice with a ouabain-BSA conjugate (Oua-BSA) and spleens cells from mice showing the "highest titer against *ouabain-BSA*" were fused to myeloma cells to generate hybridomas that produce ouabain monoclonal antibody (Lin *et al.*, page 131, column 2, emphasis added). Monoclonal antibodies produced by the hybridomas was then screened using the same antigen *i.e.*, "ouabain-BSA conjugate" (Lin *et al.*, page 131, column 2). It is well known in the art that the *carrier* of the hapten-carrier conjugate used to *screen* for antibodies having binding specificity for the hapten (*e.g.*, ouabain), should be different than the *carrier* of the hapten-carrier conjugate used to *immunize* the animal, so as to avoid selecting a mAb to the immunizing carrier (*e.g.*, BSA) or to the hapten-carrier complex (*e.g.*, ouabain-BSA). For example, Applicants direct the Examiner's attention to U.S. Patent No. 5,164,296, wherein Blaustein *et al.* clearly teach that:

> The use of a combination of ***different conjugates (containing different carriers and linking agents) is important for preparing antibodies having binding specificity for ouabain*** (Blaustein *et al.*, column 16, lines 40-43).

Lin *et al.* do ***not*** demonstrate specificity for ouabain using, for example, a competition ELISA using increasing concentrations of free ouabain. It is likely that the monoclonal antibody of Lin *et al.* recognizes BSA and that the positive findings in the human serum studies (Lin *et al.*, page 132, column 2) are due to cross-reactivity with human serum albumin (HSA), which shares many epitopes with BSA.

Furthermore, in the specification as filed, Applicants used a method similar to the one employed by Lin *et al.* except that Applicants *screened* for antibodies having binding specificity for the hapten using a *carrier* in the hapten-carrier conjugate (*i.e.*, Oua-BGG) that was different than the *carrier* of the hapten-carrier conjugate (*i.e.*, Oua-BSA) used to *immunize* the animal in an attempt to obtain a ouabain mAb. See, for example, the specification, page 18, lines 8-11 and page 19, lines 1-5 and Applicants' subsequent publication of their data in Parharmi-Seren, P., *et al., J. Immunol., 163:*4360-4366; reference AR on PTO form 1449 (Parharmi-Seren *et al.*, page 4361, column1 under the heading *"Immunizations and fusion"* and page 4261, column 2 under

the haeding *"Affinity determinations"*). However, Applicants encountered problems. In particular, Applicants teach that:

> Fusion of the spleen cells of mice immunized with Oua coupled to BSA, HSA or BGG with plasmacytomas, yielded a very large number of clones secreting mAbs specific for the Oua-protein carrier. In every fusion three kinds of specificities could be detected: The first group (32%) secreted Abs that bound to Oua-protein conjugates; they did not cross react with either Dig-protein conjugates or protein carriers alone. The specificity of the second group of mAbs which constituted 54% of the clones was directed against Oua-protein conjugates which cross reacted with Dig-proteins but not with protein carrier. The third group of mAbs (14%) bound only the protein carrier. The binding of mAbs to Oua-protein conjugates could not be inhibited by μM concentrations of free Oua. Since high affinity Abs were desired, all the inhibition screenings were performed in the presence of 100 μM free Oua. This indicated that either Oua is not immunogenic *in vivo* or the immunogenicity of the protein carriers is greater than that of Oua thus shifting the specificity of the Abs towards the protein (specification, page 25, lines 4-16).

Applicants further teach that:

> To avoid the problems associated with protein carrier immunogenicity, Oua was coupled to 26-10 Ab. ***Since the 26-10 Ab was derived from A/J mice, the same mouse strain was used for immunization with the Oua-26-10 conjugate***. Among 60 clones which secreted mAbs exhibiting specific binding to Oua-BGG only the binding of 4 Abs was inhibited with free Oua. (specification, page 25, lines 17-21, emphasis added).

Thus, to overcome the low affinity of the mAbs to ouabain obtained using a method similar to the Lin *et al.* method, Applicants employed an immunogen in which ouabain is conjugated to a carrier that is not recognized as foreign in the animal. Furthermore, Applicants screened for a mAb having binding specificity for ouabain using ouabain-BGG (*i.e.,* a hapten-carrier conjugate in which the carrier is different than the *carrier* of the hapten-carrier conjugate used to *immunize* the animal).

Applicants performed a competition ELISA using increasing concentrations of ouabain (specification, page 21, line 26 through page 22, line 5) to demonstrate that the monoclonal antibody or antigen binding fragment thereof had binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin in the case of antibodies 7-1, 1-10 and 8E4 (specification, page 22, line 20) and 50 100μM of digoxin in the case of 5A12 (specification, Figure 3). Applicants also performed

fluorescence quenching analysis which further demonstrated the specificity of the antibodies (specification, page 23, lines 14-23).

Clearly, Lin *et al.* do not anticipate Applicants' claimed monoclonal antibody.

Rejection of Claims 1, 3, 4, 38 and 39 under 35 U.S.C. §103(a)

Claims 1, 3, 4, 38 and 39 are rejected under 35 U.S.C. §103(a) as being unpatentable over Blaustein (U.S. Patent No. 5,164,296) in view of Lin *et al.* (as above) and Blaustein *(Kidney International 49*:1748-1753 (1996)). The Examiner states that Blaustein "teaches an antibody having specificity for ouabain" (Office Action, page 11) and methods of diagnosing hypertension, monitoring hypertension and treating hypertension using said antibody (Office Action, page 12). The Examiner notes that the Blaustein *et al.* do "not teach an antibody that does not cross react with digoxin" (Office Action, page 12). The Examiner refers Applicants to the discussion of Lin *et al.* as previously set forth, and further for the teaching of "the presence of endogenous digoxin in human serum" (Office Action, page 12). The Examiner cites Blaustein *(Kidney International 49*:1748-1753 (1996), referred to herein as Blaustein (1996)) as teaching "that elevated levels of endogenous ouabain play a central role in the pathogenesis of hypertension" (Office Action, page 12).

It is the Examiner's opinion that:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of US Patent No. 5,164,296 to screen the monoclonal antibodies of US Patent No. 5,164,296 for antibodies that do not cross react with digoxin because US Patent No. 5, 164,296 specifically teaches that the antibodies of the invention are useful for diagnosing and monitoring hypertension in human tissues and fluids and specifically teaches that the antibodies must have low cross-reactivity that is on the order of 1.0% or less cross-reactivity which reads on no cross reactivity and because Blaustein teaches that elevated levels of endogenous ouabain play a central role in the pathogenesis of hypertension and because US Patent 5, 164,296 specifically teaches that at the time the invention was made that is was not known that digoxin was present in human body fluids and tissues while Lin et al later teaches that digoxin is present in human fluids and tissues. Further US Patent No. 5,164,296 specifically teaches that optimization of the assays is preferred and it is clear that one of skill in the art would want to optimize the assay, given the teachings of Lin et al, in order to eliminate the artifactural binding to endogenous digoxin. One would have been motivated to screen for monoclonal antibodies that do not cross react with digoxin in order to distinguish between the cross reacting digoxin and endogenous

ouabain in order to optimize the assays and the accurate diagnosis and monitoring of hypertension in human sugjects [sic] (Office Action, page 13).

Applicants respectfully disagree. Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* There must also be motivation or suggestion in the prior art to combine elements in the prior art. That is, in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art (*In re Newell* 13 USPQ2d 1248, 1250 (Fed. Cir. 1989)).

Applicants' claimed invention is directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM of digoxin or 50μM of digoxin.

Blaustein *et al.* teach "[p]olyclonal anti-ouabain antisera" which "is ***highly specific*** for ouabain and ***other closely related cardiotonic steroids***" (Blaustein *et al.*, column 26, lines 1 and 42-43, emphasis added). In particular, Blaustein *et al.* teach that the polyclonal antisera cross reacts with digoxin at 5.2% (Blaustein *et al.*, see Table 1). As the Examiner has noted, Blaustein *et al.* teach that "an antibody having binding specificity for ouabain" is an antibody that has "low cross reactivity for the well-known steroids present in human plasma, i.e., on the order of about 1.0% or less crossreactivity, typically about 0.02 to 0.001% cross-reactivity" (Blaustein *et al.*, column 14, lines 20-29). Thus, Blaustein *et al.* do not teach 1) an anti-ouabain ***monoclonal*** antibody or 2) any antibody having ***binding specificity*** for ouabain, according to their own definition.

As discussed above, in the specification as filed, Applicants used a method similar to the employed by Lin *et al.* in an attempt to obtain a ouabain mAb, but could not obtain a monoclonal antibody which has binding specificity for ouabain and which does not cross react with digoxin.

Lin *et al.* injected Balb/C mice with a ouabain-BSA conjugate (Oua-BSA) and spleens cells from mice showing the "highest titer against *ouabain-BSA*" were fused to myeloma cells to

generate hybridomas that produce ouabain monoclonal antibody (Lin *et al.*, page 131, column 2, emphasis added). Monoclonal antibodies produced by the hybridomas was then screened using the same antigen *i.e.*, "ouabain-BSA conjugate" (Lin *et al.*, page 131, column 2). It is well known in the art that the *carrier* of the hapten-carrier conjugate used to *screen* for antibodies having binding specificity for the hapten (*e.g.*, ouabain), should be different than the *carrier* of the hapten-carrier conjugate used to *immunize* the animal, so as to avoid selecting a mAb to the immunizing carrier (*e.g.*, BSA) or to the hapten-carrier complex (*e.g.*, ouabain-BSA). For example, Applicants direct the Examiner's attention to U.S. Patent No. 5,164,296, wherein Blaustein *et al.* clearly teach that:

> The use of a combination of ***different conjugates (containing different carriers and linking agents) is important for preparing antibodies having binding specificity for ouabain*** (Blaustein *et al.*, column 16, lines 40-43).

The Examiner states that "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of US Patent No. 5,164,296 to screen the monoclonal antibodies of US Patent No. 5,164,296 for antibodies that do not cross react with digoxin" (Office Action, page 11). However, there are no "monoclonal antibodies of US Patent No. 5,164,296" (Blaustein *et al.*). Blaustein *et al.* teach that the "antibody can be polyclonal or monoclonal" (Blaustein *et al.*, column 14, line 30), but only exemplify a [p]olyclonal anti-ouabain antisera" that does not have binding specificity for ouabain (Blaustein *et al.*, Example 2; column 26, line 1).

The court has clearly stated that an obviousness rejection based upon the modification of a reference that destroys the intent, purpose or function of the teaching in the reference is not a proper obviousness rejection (*In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984)). Blaustein *et al.* teach that use of a combination of different conjugates (containing different carriers and linking agents) is important for preparing antibodies having binding specificity for ouabain (Blaustein *et al.*, column 16, lines 40-43). Lin *et al.* did not use such a method. The obviousness rejection based on the combined teachings of Blaustein *et al.* and Lin *et al.* is not a proper obviousness rejection because the combined teaching of Blaustein *et al.* and Lin *et al.* would destroy the intent, purpose or function (*i.e.*, the use of different conjugates (containing different carriers and linking agents)) of the Blaustein *et al.* reference.

Even if one of skill in the art were to make the improper combination, the combined teachings of Blaustein *et al.* and Lin *et al.* would not render obvious Applicants' claimed invention. Although Blaustein *et al.* teach that a combination of different conjugates (containing different carriers and linking agents) is important for preparing antibodies having binding specificity for ouabain, Blaustein *et al.* also states that:

> The carriers and linking agents employed ***are not critical*** (Blaustein *et al.*, column 16, lines 50-51, emphasis added).

However, Applicants have shown that in order to obtain a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment to ouabain is not inhibited by about 100μM or 50 μM of digoxin, the selection of the carrier and linking agents used is important. As discussed above, Applicants used a method similar to the one employed by Lin *et al.* except that Applicants *screened* for antibodies having binding specificity for the hapten using a *carrier* in the hapten-carrier conjugate (Oua-BGG) that was different than the *carrier* of the hapten-carrier conjugate (Oua-BSA) used to *immunize* the animal in an attempt to obtain a ouabain mAb. ***That is, Applicants used the method Blaustein et al. recommends in an attempt to obtain a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain.*** However, Applicants encountered problems. Applicants teach that:

> To avoid the problems associated with protein carrier immunogenicity, Oua was coupled to 26-10 Ab. ***Since the 26-10 Ab was derived from A/J mice, the same mouse strain was used for immunization with the Oua-26-10 conjugate.*** Among 60 clones which secreted mAbs exhibiting specific binding to Oua-BGG only the binding of 4 Abs was inhibited with free Oua. (specification, page 25, lines 17-21, emphasis added).

Thus, Blaustein *et al.* teach away from Applicants' claimed invention.

Blaustein (1996) do not provide the teachings that are lacking in the Blaustein *et al.* and Lin *et al.* references to render obvious Applicants' claimed invention. Blaustein (1996) describes "evidence that elevated levels of a recently-discovered adrenal cortical hormone, endogenous ouabain, plays a central role" in the pathogenesis of hypertension (Blaustein (1996), abstract). Blaustein (1996) does not teach or suggest anti-ouabain antibodies.

The combined teachings of Lin *et al*, Blaustein *et al.* and Blaustein (1996)do not render obvious Applicants' claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: October 9, 2002

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 8, lines 17 through 25 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The invention also embodies monoclonal antibodies or antigen binding fragments thereof which have binding specificity for ouabain and do not cross react with digoxin, expressed by or derived from cell lines deposited with the A.T.C.C., 10801 University Boulevard, Manassass, VA, 02110-2209, on October 1, 1999, designated A.T.C.C. Nos. [_____] PA-812, PA-813, PA-814 and PA-815. The cell lines which express the anti-ouabain monoclonal antibody deposited with the A.T.C.C. are designated as B cell hybridomas from spleen cells of A/J mice which express (produce) the anti-ouabain monoclonal antibody (e.g., 1-10 α oua mAb, 7-1 α oua mAb, 5A12 α oua mAb and 8E4α oua mAb) of the IgG1, κ or IgG2b, κ isotype.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment [does] to ouabain is not [crossreact with] inhibited by about 100μM of digoxin.

2. (Amended) The monoclonal antibody of Claim 1 selected from the group consisting of: 1-10 (A.T.C.C. Accession Number PTA-814), [5A12,] 7-1 (A.T.C.C. Accession Number PTA-813), 8E4 (A.T.C.C. Accession number PTA-815) and an antigen binding fragment thereof.

5. (Amended) A monoclonal antibody or antigen binding fragment thereof having the same binding specificity as a monoclonal antibody selected from the group consisting of: 1-10

(Accession Number PTA-814), [5A12,] 7-1 (A.T.C.C. Accession Number PTA-813), [and] 8E4 (A.T.C.C. Accession Number PTA-815) and an antigen binding fragment thereof, wherein the antibody binds ouabain and binding of the antibody to ouabain is not inhibited by about 100μM digoxin.

6. (Amended) A hybridoma cell line which produces a monoclonal antibody selected from the group consisting of: 1-10 (A.T.C.C. Accession Number PTA-814), [5A12,] 7-1 (A.T.C.C. Accession Number PTA-813), 8E4 (A.T.C.C. Accession Number PTA-815), a monoclonal antibody having the same binding specificity as 1-10 (A.T.C.C. Accession Number PTA-814), [5A12,] 7-1 (A.T.C.C. Accession Number PTA-813) or 8E4 (A.T.C.C. Accession Number PTA-815), and an antigen binding fragment thereof, wherein the antibody binds ouabain and binding of the antibody to ouabain is not inhibited by about 100μM digoxin.

38. (Amended) A pharmaceutical composition comprising a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen binding fragment [does] to ouabain is not [cross react with] inhibited by about 100μM of digoxin, and a pharmaceutical acceptable carrier.